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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/655,762	09/05/2003	Charles R. Cantor	701586-053023	6905
50607	7590	07/20/2006	EXAMINER	
RONALD I. EISENSTEIN 100 SUMMER STREET NIXON PEABODY LLP BOSTON, MA 02110			KIM, YOUNG J	
			ART UNIT	PAPER NUMBER
			1637	

DATE MAILED: 07/20/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

**Office Action Summary****Application No.**

10/655,762

**Applicant(s)**

CANTOR ET AL.

**Examiner**

Young J. Kim

**Art Unit**

1637

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 17 May 2006.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-8 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-8 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)  | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)   | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)             |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)<br>Paper No(s)/Mail Date <u>6/23/06</u> . | 6) <input type="checkbox"/> Other: _____  |

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### **DETAILED ACTION**

The present Office Action is responsive to the Amendment received on May 17, 2006.

#### ***Preliminary Remark***

Claim 9 has been canceled.

Claims 1-8 are pending and are under prosecution herein.

#### ***Information Disclosure Statement***

The IDS received on May 17, 2006 is acknowledged.

A signed copy of the PTO-1449 is enclosed herewith.

#### ***Drawings***

The drawings received on May 17, 2006 are acceptable.

#### ***Claim Rejections - 35 USC § 112***

The rejection of claims 1-9 under 35 U.S.C. 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter, made in the Office Action mailed on January 17, 2006 is withdrawn in view of the Amendment received on May 17, 2006.

#### ***Rejection, New Grounds – Necessitated by Amendment***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

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Claim 1, on step (a), recites that the standard nucleic acid has a nucleotide sequence that is "one base different than the target nucleic acid."

However, on step (c) of claim 1, the claim recites that, "the difference created by the at least one base between the standard and the target nucleic acid can be detected," which broadens the structure of the standard nucleic acid which was previously defined.

Claims 2-8 are indefinite by way of their dependency on claim 1.

### ***Claim Rejections - 35 USC § 102***

The rejection of claim 9 under 35 U.S.C. 102(b) as being anticipated by Bunn et al. (U.S. Patent No. 5,213,961, issued May 25, 1993), made in the Office Action mailed on January 17, 2006 is withdrawn in view of the Amendment received on May 17, 2006, canceling the rejected claim.

The rejection of claim 9 under 35 U.S.C. 102(b) as being anticipated by Arnold et al. (WO 00/50869, published August 31, 2000), made in the Office Action mailed on January 17, 2006 is withdrawn in view of the Amendment received on May 17, 2006, canceling the rejected claim.

### ***Rejections, Maintained***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The rejection of claims 1, 3, 5, and 7 under 35 U.S.C. 102(b) as being anticipated by Bunn et al. (U.S. Patent No. 5,213,961, issued May 25, 1993), made in the Office Action mailed on January 17, 2006 is ***maintained*** for the reasons of record.

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The rejection of claim 6 is included herein as being necessitated by amendment.

Applicants' arguments presented in the Amendment received on May 17, 2006 have been fully considered but they are not found persuasive for the reasons set forth in the, "Response to Arguments" section.

The Rejection:

Bunn et al. disclose a method of quantifying the amount of a target nucleic acid sequence in a biological sample (column 3, lines 24-26; column 3, lines 46-48), wherein said method comprises the steps of:

a) preparing a sample by adding a known amount of a standard nucleic acid (column 5, lines 25-27, 33, and 34), having a nucleotide sequence at least one base different than the target nucleic acid sequence (column 5, line 67 to column 6, line 20, specifically, line 17-18), which creates a site of differentiation between the target and the standard nucleic acid;

b) amplifying the sample of step (a) (column 6, lines 38-40);

c) enhancing the difference between the standard and the target nucleic acid sequence at the site of differentiation (column 6, lines 58-61); and

d) quantifying the enhanced products by measuring the ratio of the amplified target nucleic acid to the amplified standard nucleic acid to measure the amount of target nucleic acid sequence present in the biological sample (column 8, lines 39-45), thereby clearly anticipating claim 1.

With regard to claim 3, the artisans recite that the target nucleic acid could be an mRNA transcript (column 8, lines 52-54).

With regard to claims 5 and 7, the amplification of the target nucleic acid and the standard nucleic acid would result in an increased product which differ in their sequence, and therefore, arguably, enhances differences. In other words, amplification and enhancing is achieved in a single

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step. The hybridization of the primers could occur in both of the nucleic acid samples, and since the specification does not clearly define what is considered to be a “site of differentiation,” the limitation would also be anticipated.

With regard to claim 6, the standard nucleic acid, after amplification, is cleaved with a restriction enzyme, wherein the standard nucleic acid contains a sequence different from that of the target, said difference resulting in a restriction enzyme recognition site (column 6, lines 17-21).

Therefore, the invention as claimed is clearly anticipated by Bunn et al.

Response to Arguments:

On page 5 of the Response, Applicants contend that the template of Bunn does not have essentially the same sequence as the standard, which means that the PCT [*sic*] amplification will not be virtually identical.

Initially, the claims as amended are much narrower than what Applicants are arguing. Claims now require that the standard nucleic acid have one nucleotide difference from that of the target nucleic acid, and not essentially the same.

Contrary to Applicants’ assertion, Bunn et al. do disclose that the competitive template (or standard nucleic acid) nucleic acid is, “altered, mutated, such that it is now distinguishable from the target’s template.” (column 6, lines 1-3).

Bunn et al. clearly state that such alteration includes a mutation to create a new restriction endonuclease site (column 6, lines 4-5), wherein the artisans explicitly state that substitution suitable in the methods of the invention can be prepared in most cases by a single base pair change, (column 6, lines 15-17), wherein the artisans preferably and explicitly recite that, “a single base pair change alters or creates a restriction enzyme site...[which] may be used to distinguish the competitive template from the target template following the amplification.” (column 6, lines 17-21).

Applicants contend that the present method is used with essentially two consecutive amplification steps (page 5, bottom paragraph, Response).

Applicants are advised that the claims do not recite two consecutive amplification steps, but rather a single amplification step and a step “generically” recited as that which enhances the difference between the standard and the target nucleic acid. Such are not the same.

While the claims are read in light of the specification, it is improper to read limitation from the specification into the claims when such limitations are not actively recited.

Again, Applicants appear to contend that the second “amplification” step further enhances by specifically amplifying the difference (page 5, bottom paragraph, Response).

Again, this not true, because the claims do not recite such steps.

In addition, the restriction digest of the amplified products formed from the amplification of target nucleic acid and the competitive nucleic acid template, would clearly anticipate a generic step reciting that the difference between the standard and the target nucleic acid at the site results in enhanced products so that the difference created by the at least one base between the standard and the target nucleic acid can be detected.

With regard to claim 6, the claim has been amended from a method which utilizes an allele-specific enzyme to, “an enzyme that specifically cleaves a the site of differentiation.”

As previously discussed as well as on column 6, lines 38-45 of Bunn et al. the artisan explicitly teach the cleavage of the amplified competitive template nucleic acid, wherein the cleavage occurs at the site of differentiation created by substitution of single nucleotide resulting in a restriction site.

Clearly, Bunn et al. anticipate the invention as claimed.

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Claims 1, 3, and 6 are rejected under 35 U.S.C. 102(b) as being anticipated by Becker et al. (Nucleic Acids Research, 1989, vol. 17, no. 22, pages 9437-9446; IDS ref).

Becker et al. disclose a method of measuring the amount of target nucleic acid sequence in a biological sample, comprising the steps:

a) preparing a sample by adding known amount of a standard nucleic acid, wherein said standard nucleic acid has a single nucleotide sequence difference from the target nucleic acid (page 9437, bottom paragraph, in the phrase, "mutated cDNA serves as internal standard"; and page 9438, 2<sup>nd</sup> paragraph; Figure 1);

b) amplifying the sample of step (a) (see Figure 1, via PCR);

c) using a further method to enhance the difference between the standard and the target nucleic acid sequence at the site resulting in enhanced products so that the difference created by the at least one base between the standard and the target nucleic acid can be detected (the digestion step of Figure 1 which enhances the difference between the standard and the target nucleic acid);

d) quantifying the enhanced products of step (c) by measuring the ratio of the amplified target nucleic acid to the amplified standard nucleic acid to measure the amount of target nucleic acid present in the sample (Figure 2; page 9442, bottom paragraph).

With regard to claim 3, the target nucleic acid is mRNA (page 9437, 2<sup>nd</sup> paragraph).

With regard to claim 6, the enhancement is achieved via an enzyme which specifically cleaves at the site of differentiation (*Eco*RI digestion; page 9442, bottom paragraph).

### ***Claim Rejections - 35 USC § 103 - Maintained***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the



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subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The rejection of claim 2 under 35 U.S.C. 103(a) as being unpatentable over Bunn et al. (U.S. Patent No. 5,213,961, issued May 25, 1993) in view of Carroll et al. (U.S. Patent No. 5,906,744, issued May 25, 1999), made in the Office Action mailed on January 17, 2006 is maintained for the reasons of record.

Applicants' arguments presented in the Amendment received on May 17, 2006 have been fully considered but they are not found persuasive for the reasons set forth in the, "Response to Arguments" section.

The Rejection:

Bunn et al. disclose a method of quantifying the amount of a target nucleic acid sequence in a biological sample (column 3, lines 24-26; column 3, lines 46-48), wherein said method comprises the steps of:

a) preparing a sample by adding a known amount of a standard nucleic acid (column 5, lines 25-27, 33, and 34), having a nucleotide sequence at least one base different than the target nucleic acid sequence (column 5, line 67 to column 6, line 20, specifically, line 17-18), which creates a site of differentiation between the target and the standard nucleic acid;

b) amplifying the sample of step (a) (column 6, lines 38-40);

c) enhancing the difference between the standard and the target nucleic acid sequence at the site of differentiation (column 6, lines 58-61); and

d) quantifying the enhanced products by measuring the ratio of the amplified target nucleic acid to the amplified standard nucleic acid to measure the amount of target nucleic acid sequence present in the biological sample (column 8, lines 39-45).

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The artisans recite that the target nucleic acid could be an mRNA transcript (column 8, lines 52-54).

The amplification of the target nucleic acid and the standard nucleic acid would result in an increased product which differ in their sequence, and therefore, arguably, enhances differences. In other words, amplification and enhancing is achieved in a single step. The hybridization of the primers could occur in both of the nucleic acid samples, and since the specification does not clearly define what is considered to be a "site of differentiation," the limitation would also be anticipated.

The standard nucleic acid, after amplification, is cleaved with a restriction enzyme, wherein the standard nucleic acid contains a sequence different from that of the target, said difference resulting in a restriction enzyme recognition site (column 6, lines 17-21).

Bunn et al. do not explicitly teach that a target nucleic acid from an infectious agent should be employed in their method (claim 2).

Carroll et al. disclose that amplification techniques such as PCR, branched DNA, and nucleic acid sequence based amplification (NASBA) is employed commonly in the art to detect the levels of infectious agents in samples (column 1, lines 23-29, lines 55-56).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to apply the amplification method of Bunn et al. and apply it for quantifying the levels of infectious agents in samples, as the desire to do so have been long-felt and well-established in the art (diagnosis and prognosis of infectious diseases). Thus, one of ordinary skill in the art would have been motivated to employ the method of Bunn et al. so as to determine the levels of infectious agents in a sample. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success at combining the teachings, for any known quantification method via amplification, as clearly expressed by Carroll et al., would have sufficed.

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Therefore, the invention as claimed is *prima facie* obvious over the cited references.

Response to Arguments:

All of Applicants' arguments are directed toward the teachings of Bunn et al. which have been fully rebutted above. Since Applicants do not present any new argument directed to the instant rejection, the rejection is maintained for the reasons already of record.

***Rejections, New Grounds – Necessitated by IDS***

Claim 2 is rejected under 35 U.S.C. 103(a) as being unpatentable over Becker et al. (Nucleic Acids Research, 1989, vol. 17, no. 22, pages 9437-9446; IDS ref) in view of Carroll et al. (U.S. Patent No. 5,906,744, issued May 25, 1999).

The teachings of Becker et al. have already been discussed above.

Becker et al. do not explicitly teach that a target nucleic acid from an infectious agent should be employed in their method (claim 2).

Carroll et al. disclose that amplification techniques such as PCR, branched DNA, and nucleic acid sequence based amplification (NASBA) is employed commonly in the art to detect the levels of infectious agents in samples (column 1, lines 23-29, lines 55-56).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to apply the amplification method of Becker et al. and apply it for quantifying the levels of infectious agents in samples, as the desire to do so have been long-felt and well-established in the art (diagnosis and prognosis of infectious diseases). Thus, one of ordinary skill in the art would have been motivated to employ the method of Becker et al. so as to determine the levels of infectious agents in a sample. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success at combining the teachings, for any

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known quantification method via amplification, as clearly expressed by Carroll et al., would have sufficed.

Therefore, the invention as claimed is *prima facie* obvious over the cited references.

Claims 4, 5, 7, and 8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Becker et al. (Nucleic Acids Research, 1989, vol. 17, no. 22, pages 9437-9446; IDS ref) in view of Amexis et al. (PNAS, October 2001, vol. 98, no. 21, pages 12097-12102).

Becker et al. disclose a method of measuring the amount of target nucleic acid sequence in a biological sample, comprising the steps:

a) preparing a sample by adding known amount of a standard nucleic acid, wherein said standard nucleic acid has a single nucleotide sequence difference from the target nucleic acid (page 9437, bottom paragraph, in the phrase, "mutated cDNA serves as internal standard"; and page 9438, 2<sup>nd</sup> paragraph; Figure 1);

b) amplifying the sample of step (a) (see Figure 1, via PCR);

c) using a further method to enhance the difference between the standard and the target nucleic acid sequence at the site resulting in enhanced products so that the difference created by the at least one base between the standard and the target nucleic acid can be detected (the digestion step of Figure 1 which enhances the difference between the standard and the target nucleic acid);

d) quantifying the enhanced products of step (c) by measuring the ratio of the amplified target nucleic acid to the amplified standard nucleic acid to measure the amount of target nucleic acid present in the sample (Figure 2; page 9442, bottom paragraph).

The target nucleic acid is mRNA (page 9437, 2<sup>nd</sup> paragraph).

The enhancement is achieved via an enzyme which specifically cleaves at the site of differentiation (*EcoRI* digestion; page 9442, bottom paragraph).

Becker et al. do not employ mass spectrometry in their quantification method (claims 4 and 8).

Becker et al. do not explicitly disclose a method of performing primer extension at the site of differentiation (claim 5), or allele-specific hybridization at the site of differentiation (claim 7).

Amexis et al. disclose a method of quantifying a target nucleic acid in a sample, wherein the method comprises the steps of:

- a) amplification of a target nucleic acid with a pair of primers (Figure 1B; page 12098, 2<sup>nd</sup> column, 3<sup>rd</sup> paragraph);
- b) amplifying the amplified product with MassExtend primers which is specific for a point mutation (Figure 1B; page 12098, 2<sup>nd</sup> column, 3<sup>rd</sup> paragraph (middle)); and
- c) detecting and quantifying the amplified products (Figure 1B; page 12098, 2<sup>nd</sup> column, 3<sup>rd</sup> paragraph (bottom); Abstract; page 12098, 1<sup>st</sup> column, 3<sup>rd</sup> paragraph).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Becker et al. and with the teachings of Amexis et al., thereby arriving at the claimed invention for the following reasons.

The method employed by Becker et al., which is drawn to the amplifying the target nucleic acid and the standard nucleic acid (which contains a single nucleotide mutation) via use of primers which flank the target nucleic acid region, employs more than a decade old technique – that is – restriction digest, electrophoresis, followed by the radiolabeled (<sup>32</sup>P) quantitation method.

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Thus, one of ordinary skill in the art at the time the invention was made would have been motivated to employ a non-radioactive method of accurately quantitating the target nucleic acid, such as MALDI-TOF, thereby arriving at the claimed invention.

One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success at combining the teachings since methods of quantification employing mass spectrometry, such as SNuPE (single nucleotide primer extension), have been well-established. Given the fact that Amexis et al. amplify a known target nucleic acid sequence via use of a flanking primer pairs, followed by the mutation-specific primer extension, one of ordinary skill in the art would have recognized that the amplification products of Becker et al., would have served equally well for the mutation-specific primer extension, which would have been necessary for the subsequent mass spectrometric analysis.

Therefore, the invention as claimed is *prima facie* obvious over the cited references.

### ***Conclusion***

No claims are allowed.

Applicant's submission of an information disclosure statement under 37 CFR 1.97(c) with the fee set forth in 37 CFR 1.17(p) on June 23, 2006 prompted the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 609.04(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be

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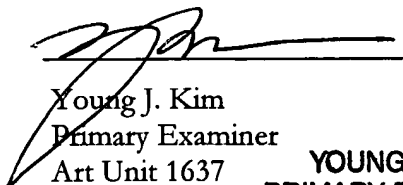
calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

### *Inquiries*

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Young J. Kim whose telephone number is (571) 272-0785. The Examiner is on flex-time schedule and can best be reached from 8:30 a.m. to 4:30 p.m (M-W and F). The Examiner can also be reached via e-mail to Young.Kim@uspto.gov. However, the office cannot guarantee security through the e-mail system nor should official papers be transmitted through this route.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Dr. Gary Benzion, can be reached at (571) 272-0782.

Papers related to this application may be submitted to Art Unit 1637 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant does submit a paper by FAX, the original copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office. All official documents must be sent to the Official Tech Center Fax number: (571) 273-8300. For Unofficial documents, faxes can be sent directly to the Examiner at (571) 273-0785. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

  
Young J. Kim  
Primary Examiner  
Art Unit 1637  
7/17/2006

**YOUNG J. KIM  
PRIMARY EXAMINER**

YJK